2011

Prevalence of Metabolic Abnormalities in Children with Varying Degrees of Obesity

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June 10, 2011

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Abstract

As the prevalence of obesity among children has risen, metabolic syndrome, a cluster of abnormalities which includes obesity, altered glucose metabolism, hypertension, and dyslipidemia, has increasingly become recognized in the pediatric population. Metabolic syndrome has been studied extensively in adults, and there is increasing interest to understand the condition in adolescents; however, studies of metabolic syndrome in younger children are limited. The purpose of this study is to examine the prevalence of metabolic syndrome and its individual components among children aged 6-10 years. Demographic, anthropometric, and biochemical data were gathered retrospectively from the medical records of 222 obese children aged 6-10 years who were seen as new patients in a hospital-based clinic for management of obesity and related conditions. The results of this study suggest that the study population is at high risk of morbidity; 77.9% of subjects had at least one metabolic abnormality in addition to obesity, and 27.9% of subjects in this study had metabolic syndrome. This study found a high risk of elevated systolic blood pressure and elevated fasting insulin in the study population, with 63.1% of subjects having prehypertension or hypertension and 40.1% of subjects having elevated fasting insulin. The results of this study suggest that current recommendations for screening of metabolic abnormalities in obese school-age children are not sufficiently aggressive. Current standards of practice do not include assessment for metabolic syndrome components in children under the age of 10 years, with the exception of blood pressure. The prevalence of impaired glucose metabolism, insulin resistance, and dyslipidemia, however, is significant in this population, and screening for these abnormalities in children under the age of 10 is warranted.

Introduction: The Problem and its Scope

The prevalence of obesity among children has increased rapidly over the past 30 years. In the United States between 1974 and 2004, rates of obesity have risen from 4.0% to 18.8% among children aged 6 to11 years (National Center for Health Statistics). This increase is of great public health concern as obese children are at higher risk for a variety of metabolic, psychological, orthopedic, respiratory, and cardiovascular conditions (Daniels, 2006).

One condition commonly associated with adult obesity is metabolic syndrome, a cluster of abnormalities which includes altered glucose metabolism, hypertension, and dyslipidemia (Steinberger, 2003). Metabolic syndrome is associated with increased risk of several chronic illnesses. For example, adults with metabolic syndrome are five times more likely to develop type 2 diabetes and three times more likely to develop cardiovascular disease than their counterparts who do not have metabolic syndrome (Zimmet et al., 2007).

As the prevalence of childhood obesity has risen, metabolic syndrome has increasingly become recognized in the pediatric population. The overall prevalence of a metabolic syndrome phenotype among U.S. adolescents aged 12-19 years increased from 4.2% in 1988-1992 to 6.4% in 1999-2000 in one survey (Duncan, Li, & Zhou, 2004). In the same survey, the prevalence of metabolic syndrome among obese adolescents (BMI $\geq 95^{th}$ percentile for age) was 32.1%. Metabolic syndrome in childhood and adolescence is a strong risk factor for chronic illness in these age groups (Calcaterra et al., 2008). In multiple studies, obese children who had components of metabolic syndrome exhibited cardiovascular pathology such as increased carotid intima-media thickness and enlarged left ventricular wall thickness (Kapiotis et al., 2006; Chinali et al., 2008).

Metabolic syndrome has been studied extensively in adults, and there is increasing interest to understand this condition in adolescents; however, studies of metabolic syndrome in younger children are limited. If obese adolescents and adults are at risk of developing multiple metabolic abnormalities which increase the potential for cardiovascular disease, it seems plausible that obese younger children may share the same risk profile. In fact, development of risk factors early in life may result in earlier onset of cardiovascular disease and poorer outcomes due to longer duration of exposure (Halpern et al., 2010). Therefore, it is necessary to explore the prevalence and effects of metabolic abnormalities in young obese children.

Statement of Purpose

The purpose of this study is to describe the prevalence of metabolic syndrome and its individual components among overweight and obese children aged 6-10 years. In addition, this study will explore how the prevalence of metabolic syndrome, prevalence of individual metabolic abnormalities, and number of metabolic abnormalities per individual varies with severity of obesity in this population.

Review of Literature

Pediatric Metabolic Syndrome and Adult Morbidity

Childhood metabolic syndrome tracks into adulthood and is a risk factor for adult diseases. In a study by Morrison, Friedman, and Gray-McGuire (2007) which followed 6-19 year old children over more than 20 years, 68% of subjects with pediatric metabolic syndrome had metabolic syndrome as adults. In another study which followed 9-18 year old children for 14-27 years, youth with metabolic syndrome had a 2.7-3.4 times higher risk of developing adult metabolic syndrome compared to youth without metabolic syndrome (Magnussen et al., 2010). Finally, in a study by Chen, Srinivasan, Li, Xu, and Berenson (2005), children with three or more metabolic syndrome components in the bottom quartile among study subjects had significantly lower prevalence of adult metabolic syndrome than children with less than three risk variables in the bottom quartile.

There are multiple factors which affect the tracking of metabolic syndrome from childhood to adulthood. The more obese a child is at baseline measurement, the more likely he or she is to develop metabolic syndrome later in life (Bao, Srinivasan, Wattigney, & Berenson, 1994; Whitlock, Williams, Gold, Smith, & Shipman, 2005). In a 2007 study by Morrison and colleagues, for each 10-point increase in age-specific BMI percentile at baseline, the risk of adult metabolic syndrome increased by 24%. Greater increase in BMI over time is also associated with greater stability in the metabolic syndrome diagnosis (Bao et al., 1994; Weiss, Shaw, Savoye, & Caprio, 2009). In a 2009 study by Weiss and colleagues, all subjects without metabolic syndrome at baseline who developed it at follow up had either maintained or increased their BMI z-score. Conversely, 84% of subjects who had metabolic syndrome in childhood but not at follow up had either decreased or maintained their BMI z-score.

Tracking of metabolic syndrome from childhood to adulthood is also associated with age at baseline and number of cardiometabolic abnormalities in childhood. The later in childhood a young person has metabolic syndrome, the more likely he or she is to maintain the diagnosis as an adult (Bao et al., 1994; Whitlock et al., 2005). In addition, the risk of adult metabolic syndrome increases as the number of metabolic syndrome components in youth increases (Magnussen et al., 2010; Weiss et al., 2009).

Childhood metabolic syndrome is associated with adult morbidity. In one study by Morrison, Friedman, Wang, and Gluek (2008), a diagnosis of metabolic syndrome in childhood resulted in an 11-fold increase in risk of type 2 diabetes in adulthood. Diagnosis of pediatric metabolic syndrome is also associated with development of cardiovascular disease. In one study, diagnosis of pediatric metabolic syndrome was associated in two-fold higher risk of developing an increase in carotid intima-media thickness in adulthood, a sign of atherosclerosis (Magnussen et al., 2010). In another study which followed 6-19 year old children over more than 20 years, the incidence of cardiovascular disease was 19.4% among adults who had metabolic syndrome as children, and only 1.5% among adults without metabolic syndrome as children (Morrison, Friedman, & Gray-McGuire, 2007).

Defining Metabolic Syndrome

The identification of metabolic abnormalities is extremely important in determining cardiovascular risk in children; however, diagnosis of metabolic syndrome is difficult as there is currently no consistent, accepted definition for the condition in pediatrics. In adults, metabolic syndrome is typically defined using sets of diagnostic criteria from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), the World Health Organization, (WHO), or the International Diabetes Foundation (IDF). While these criteria

differ slightly, they all utilize a measure of body fatness, hypertension, dyslipidemia, and glucose intolerance (Battista, Murray, & Daniels, 2009). The following table summarizes the ATP III, WHO, and IDF diagnostic criteria for adults.

Table 1
Selected diagnostic criteria for metabolic syndrome in adults.

NCEP ATP III	WHO	IDF
		Waist circumference of ≥ 94 cm for Europid males ≥ 80 cm for Europid females *(Other ethnicity-specific waist circumferences are available)*
≥ 3 of the following:	**Plus ≥ 2 of the following:**	**Plus ≥ 2 of the following:**
Waist circumference of > 102 cm for males > 88 cm for females	BMI > 30 kg/m^2 *and/or* Waist-to-hip ratio of > 0.9 for males > 0.85 for females	
Triglycerides > 150 mg/dL	Triglycerides > 150 mg/dL *and/or* HDL < 35 mg/dL for males HDL < 39 mg/dL for females	Triglycerides ≥ 150 mg/dL *Or specific treatment for this abnormality.*
HDL < 40 mg/dL for males HDL < 50 mg/dL for females		HDL < 40 mg/dL for males HDL < 50 mg/dL for females *Or specific treatment for this abnormality.*
Systolic BP ≥ 130 mm/Hg Diastolic BP ≥ 85 mm/Hg	Systolic BP > 140 mm/Hg Diastolic BP > 90 mm/Hg	Systolic BP ≥ 130 mm/Hg or Diastolic BP ≥ 85 mm/Hg *Or specific treatment for previously-diagnosed hypertension.*
Fasting glucose ≥110 mg/dL		Fasting glucose ≥100 mg/dL *Or previously-diagnosed type 2 diabetes.*
	Urinary albumin excretion rate ≥ 20 µg/min *Or* Albumin: creatinine ratio ≥ 30 mg/g	

(National Cholesterol Education Program, 2001; Alberti & Zimmet, 1998; International Diabetes Federation, 2005)

Criteria for metabolic syndrome in adults have been adapted for use in children by utilizing age and sex-specific cutoffs for different metabolic parameters; however, adaptation is difficult due to a variety of factors. Because children and adolescents are growing and changing rapidly, singular cut-points for risk factors such as hypertension cannot be applied across the pediatric population. In addition, the physiological insulin resistance of puberty confounds measures of glucose intolerance in this population (Steinberger et al., 2009). Finally, waist circumference, which is a key measure of abdominal adiposity in adult criteria, is not commonly used in children. Although the United States, Canada, and the United Kingdom have age and sex-specific reference values for waist circumference, they have not been endorsed by any organization and, as a result, are not routinely used in clinical practice (Zimmet et al., 2007).

Adaptations of adult criteria for metabolic syndrome in children vary greatly. In a 2008 review by Ford and Li, more than 40 different definitions were found in studies of metabolic syndrome in children and adolescents. In 2007, the International Diabetes Federation attempted to establish a consensus definition, but it contained several weaknesses, including utilization of waist-circumference cutoffs and lack of criteria for children under 10 years of age (Zimmett et al., 2007). As a result, the IDF consensus definition is not widely used in clinical practice or in research.

Table 2
*International Diabetes Federation criteria of at-risk groups and metabolic syndrome in children and adolescents.**

	6 to less than 10 years of age	10 to less than 16 years of age	16 years of age and above
Obesity	Waist circumference ≥ 90th percentile for age and sex *Metabolic syndrome cannot be diagnosed, but further measurements should be made of there is a family history of obesity-related illness.*	Waist circumference ≥ 90th percentile for age and sex or adult cut-off if lower	Waist circumference of ≥ 94 cm for Europid males ≥ 80 cm for Europid females *(Other ethnicity-specific waist circumferences are available)*
Triglycerides		Triglycerides ≥ 150 mg/dL	Triglycerides ≥ 150 mg/dL *Or specific treatment for this abnormality.*
High-Density Lipoprotein (HDL)		HDL < 40 mg/dL	HDL < 40 mg/dL for males HDL < 50 mg/dL for females *Or specific treatment for this abnormality.*
Blood Pressure		Systolic BP ≥ 130 mm/Hg or Diastolic BP ≥ 85 mm/Hg	Systolic BP ≥ 130 mm/Hg or Diastolic BP ≥ 85 mm/Hg *Or specific treatment for previously-diagnosed hypertension.*
Altered Glucose Metabolism		Fasting glucose ≥100 mg/dL *Or previously-diagnosed type 2 diabetes.*	Fasting glucose ≥100 mg/dL *Or previously-diagnosed type 2 diabetes.*

* Diagnosis requires presence of abdominal obesity as measured by waist circumference plus at least two of the other four factors.

(Zimmet et al., 2007)

Table 3
Pediatric metabolic syndrome definitions in widely-cited studies.

Study	No. of Risk Factors	Obesity	Blood Pressure	Triglycerides	High-Density Lipoprotein	Glucose Intolerance
Cook et al., 2003	≥ 3	Waist circumference ≥ 90th percentile for age and sex	≥ 90th percentile for age, sex, and height	≥ 110 mg/dL	≤ 40 mg/dL	Fasting glucose ≥ 110 mg/dL
De Ferranti et al., 2004	≥ 3	Waist circumference > 75th percentile for age and sex	> 90thpercentile for age, sex, and height	≥ 100 mg/dL	< 50 mg/dL	Fasting glucose ≥ 110 mg/dL
Weiss et al., 2004	≥ 3	Body mass index z-score ≥ 2.0	> 95th percentile for age, sex, and height	> 95th percentile	< 5th percentile	Glucose 140-199 mg/dL 2 h following 75 g glucose load
Cruz et al., 2004	≥ 3	Waist circumference ≥ 90th percentile for age and sex	> 90th percentile for age, sex, and height	≥ 90th percentile	≤ 10th percentile	Glucose 140-199 mg/dL 2 h following 75 g glucose load
Ford et al., 2005	≥ 3	Waist circumference ≥ 90th percentile for age and sex	≥ 90th percentile for age, sex, and height	≥ 110 mg/dL	≤ 40 mg/dL	Fasting glucose ≥ 110 mg/dL

While a single, accepted definition would be helpful for clinicians and researchers, it is not necessary for the exploration of metabolic syndrome in children. A recent study by Rinaldi and colleagues (2010) observed great agreement among six commonly used diagnostic criteria for metabolic syndrome in children. Regardless of the definition chosen, it is widely accepted that multiple metabolic abnormalities place children at heightened cardiovascular risk. The definition chosen for metabolic syndrome is not important as long as these abnormalities are

identified and addressed. Therefore, at this time researchers and clinicians should select definitions based on the components available in a given situation.

Measures of Adiposity for Metabolic Syndrome

An essential element of any study or clinical assessment of metabolic syndrome is a measure of body fatness. However, it is difficult to directly measure body fat in clinical or community settings because accurate methods such as dual-energy x-ray absorptiometry (DEXA), hydrostatic underwater weighing (hydrodensitometry), and air displacement plethysmography are time-consuming and expensive. As a result, it is often necessary to utilize anthropometric measures such as waist circumference and body mass index (BMI) to estimate body fatness. Waist circumference will not be used as a measurement of adiposity in this study because it is not routinely collected in the clinic from which subjects will be chosen. As was mentioned above, waist circumference has not been recommended for clinical use by any professional organization because comparative standards and high-risk cutoffs have not been established (Zimmet et al., 2007).

In the clinic from which subjects will be selected, BMI is routinely used to assess adiposity. BMI is a measure of body weight adjusted for height, defined as weight in kilograms divided by the square of height in meters (kg/m^2). BMI assessment has many strengths; it is easily calculated from weight and height, which are routinely collected for most children. In addition, BMI accurately predicts body fatness (Pietrobelli et al., 1998; Mei et al., 2002). In a study which compared BMI to fat-mass index (kg fat/height^2) in children aged 5-18 years, the correlation between the two measures was very strong for overweight and obese children (r=0.85-0.96) (Freedman et al., 2005). BMI also correlates well with health risk. In a study of

children aged 9-13 years, BMI greater than the 95th percentile for age was a specific and sensitive predictor of the presence of 3 or more metabolic abnormalities (Ice et al., 2009).

The Expert Committee on the Assessment, Prevention, and Treatment of Child and Adolescent Overweight and Obesity recommends use of the Centers for Disease Control and Prevention (CDC) BMI-for-age charts to screen for excess adiposity in children and adolescents (Barlow &The Expert Committee, 2007). The CDC, American Academy of Pediatrics, and Institutes of Medicine all recommend using the 85th and 95th percentiles as cutoffs for increased health risks due to excess body weight. BMI greater than or equal to the 85th percentile but less than the 95th percentile is termed "overweight", while BMI greater than or equal to the 95th percentile is termed "obese" (Barlow & The Expert Committee, 2007).

While BMI is a very useful tool, the CDC's BMI growth curve and its cutoff points it have several disadvantages. For example, children between the 85th and 95th percentile may actually have a large amount of lean mass as opposed to fat mass, so interpretation of BMI for children who fall into this range must be done with care. In addition, the curve does not sufficiently describe risk among obese children. For example, there is a large difference in adiposity and risk of health problems between a child weighing 200 pounds and another weighing 300 pounds, but they both fall into the same risk category (BMI $\geq$ 95th percentile) (Barlow & The Expert Committee, 2007). As a result, the Expert Committee (2007) has proposed recognition of a third cutoff point, BMI $\geq$ 99thpercentile for age, which will be indicative of severe obesity.

Among individual children between the 5th and 95th percentiles for age, changes in BMI percentile can be used to monitor changes in relative adiposity. Percentiles are not useful, however, for children above the 95th percentile, because accurate percentile cutoffs are not

available. In addition, raw BMI (BMI not interpreted using a growth chart) is not useful for individual children or groups of children as a result of differences in expected BMI due to age-related growth (Woo, 2009). To remedy these particular problems, standardized measures such as BMI z-scores were developed. BMI z-scores can be used for groups of children and individuals with BMI percentiles above the 95th to describe degree of adiposity and changes in adiposity. In a study of children aged 2-5 years, BMI z-score was better than raw BMI or BMI percentile in assessing adiposity on a single occasion (Cole, 2005). In another study, which compared raw BMI and BMI z-score to measures of body fat using bioelectrical impedance, BMI z-score predicted changes in adiposity more accurately than raw BMI (Hunt, Ford, Sabin, Crowne, & Shield, 2007).

Like raw BMI and BMI percentiles, BMI z-scores have several weaknesses. BMI z-scores are difficult to calculate, interpret, and explain to families, particularly when they have limited knowledge of statistics. In addition, a 2009 paper by Woo suggests that BMI z-scores may not accurately describe changes in weight status among children and adolescents with a BMI greater than the 97th percentile for age. The statistical techniques used to correct for skewed raw BMI values in the 2000 CDC growth charts introduce systematic bias among z-scores in the upper tail of the distribution. As a result of this bias, the relationship between BMI and BMI z-score differs with age, sex, and BMI. Most notably, a stable high BMI in adolescence results in increasing BMI z-scores for boys, and decreasing BMI z-scores for girls. Woo (2009) suggests that another method may be needed to accurately describe changes in adiposity among the severely obese.

An alternative to BMI z-scores which is also useful for groups of children and individuals with BMI greater than the 95th percentile for age is relative BMI (rBMI). RBMI is calculated by

dividing the subject's actual BMI by the BMI at the 50th percentile for each subject's age and gender using data from the appropriate CDC BMI chart. Essentially, rBMI is a percentage of an "ideal" or "standard" body weight. While rBMI is not widely used in the literature to describe the severity of overweight, it has several advantages over other methods. RBMI is a simple calculation that can be easily explained to parents and caregivers. In addition, it accurately describes relative adiposity. A study by Cowan, Velasquez, Neira, Villegas-Barreto, and Tylavsky (2006) found that rBMI correlates with measures of body fat by dual energy x-ray absorptiometry in children across ages, genders, and races.

Etiology

There is much debate regarding the etiology of metabolic syndrome because several conditions, including obesity, insulin resistance, and inflammation, have been implicated in its development (Steinberger et al., 2009). It is likely that metabolic syndrome is a result of complex interactions among these conditions as well as other factors such as heredity and lifestyle, as illustrated in Figure 1.

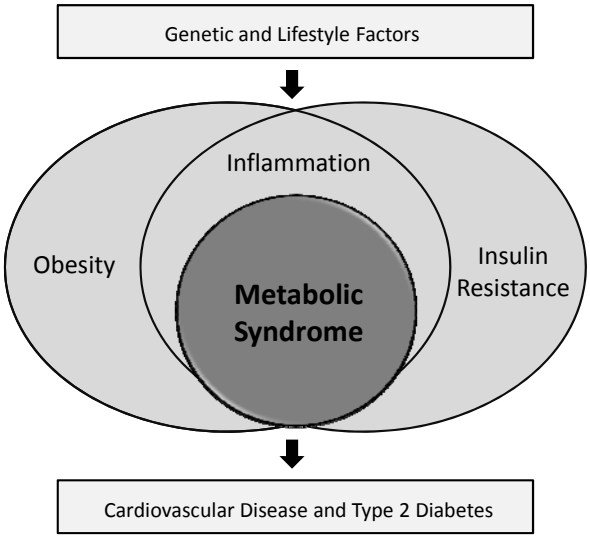

Figure 1. Complex etiology of metabolic syndrome.

While metabolic syndrome is modulated by many factors, strong evidence supports obesity as the predominant correlate of cardiometabolic risk (Goodman, Dolan, Morrison, & Daniels, 2005). Metabolic syndrome is extremely rare in normal weight children, but quite prevalent in those with excess body fat. In a study of adolescents aged 12-19 years selected from the National Health and Nutrition Examination Survey (NHANES) 1999-2000, less than 1% of normal weight subjects met the age-modified ATP III criteria for metabolic syndrome, while 32.1% of obese subjects met the criteria (Duncan et al., 2004).

Within the overweight and obese population, prevalence of metabolic syndrome rises with increasing severity of obesity. In a Turkish study which examined metabolic syndrome in obese children aged 2-19 years, body mass index (BMI) was the most important determinant of metabolic syndrome, with a one point increase in BMI z-score doubling the prevalence of the condition (Sen, Kandemir, Alikasifoglu, Gonc, & Ozon, 2008). A similar study by Weiss and colleagues (2004) which included subjects aged 4-20 years found significant increases in the prevalence of metabolic syndrome with each half-unit increase in BMI. While metabolic syndrome was absent in normal weight and overweight children, 38.7% of moderately obese subjects (defined as BMI z-score of 2.0-2.5) and 49.7% of severely obese subjects (BMI z-score greater than 2.5) met the criteria for metabolic syndrome.

Just as prevalence of metabolic syndrome is higher in obese children than in normal weight children, the prevalence of each individual abnormality associated with the syndrome is higher in obese children. In one study, prevalence of cardiometabolic risk factors including high systolic blood pressure, low HDL cholesterol, elevated triglycerides, and high insulin levels were all significantly higher among overweight and obese subjects than among normal weight subjects (Lambert et al., 2008). Similarly, prevalence of each abnormality rises with increasing severity

of obesity. In the 2004 study by Weiss and colleagues discussed above, glucose, insulin, triglycerides, blood pressure, glucose tolerance, and HDL all worsened with increasing obesity, independently of age, sex, and pubertal status.

Finally, the number of metabolic abnormalities per individual is increased among obese children, and rises with increasing severity of obesity. In Lambert and colleagues' 2008 study, the number of components of the metabolic syndrome increased significantly between normal weight and overweight children, and between overweight and obese children. In addition, obese boys were 15 times more likely and obese girls were 18 times more likely to have two or more metabolic syndrome components than their normal weight counterparts. In another study, no normal weight or overweight subjects had 3 or more metabolic abnormalities, while 12.0% of moderately obese subjects and 31.1% of severely obese subjects had 3 or more abnormalities (Calcaterra et al., 2008).

The mechanism by which obesity contributes to development of metabolic syndrome is primarily due to its promotion of insulin resistance and inflammation. Insulin resistance is a state in which usual concentrations of insulin do not adequately stimulate utilization of glucose by the liver and peripheral tissues (Matthaei, Stumvoll, Kellerer, & Haring, 2000; Weiss & Kaufman, 2008). Insulin resistance is relatively rare in the overall pediatric population, with a prevalence of about 4% (Weiss et al., 2004). It is quite common, however, among obese children and adolescents, with a prevalence estimated at 50% or above (Weiss et al., 2004). In a 2002 study examining the relationship between adiposity and insulin resistance, body fat accounted for 55% of the variance in insulin sensitivity after adjusting for age, gender, race, and pubertal stage (Caprio, 2002). In another study by Velasquez-Meiyer, Cowan, Neira, and

Tylavsky (2008), two different indices of insulin sensitivity decreased significantly as the severity of overweight increased ($p<0.01$).

Excess body fat plays an important role in the development of insulin resistance because adipose tissue releases metabolites, hormones, and cytokines that disrupt insulin action in the body (Chiarelli & Marcovecchio, 2008). For example, adipose tissue produces the inflammatory cytokines interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF- α), which disrupt insulin action and contribute to the pathogenesis of insulin resistance (Matsuzawa, 2005). Data from animal studies suggest that increased levels of resistin, another molecule produced by adipose tissue, impairs insulin sensitivity (Matsuzawa, 2005). Conversely, another cytokine called adiponectin increases insulin sensitivity and decreases the likelihood of insulin resistance. Adiponectin levels are lower in children and adolescents with greater amounts of body fat, thereby increasing the risk of insulin resistance in this population (Weiss et al., 2004).

In addition to the amount of body fat, distribution of body fat and ectopic fat deposition is implicated in the pathogenesis of insulin resistance. In a study of obese adolescent females, amount of visceral fat was directly correlated with insulin resistance, while there was no significant relationship between insulin resistance and abdominal subcutaneous fat (Caprio et al., 1995). Ectopic fat deposition in the muscle tissue is also associated with insulin resistance due to decreased glucose uptake in the muscle. In several studies, intramyocellular lipid accumulation was significantly greater in obese children with insulin resistance than in obese children with normal insulin sensitivity (Chiarelli & Marcovecchio, 2008). Finally, accumulation of fat in the liver may cause insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production (Weiss & Kaufman, 2008).

Insulin resistance contributes too many of the abnormalities associated with metabolic syndrome. Insulin resistance in the liver results in lipogenesis, contributing to dyslipidemia. Over time, individuals with insulin resistance develop chronic hyperinsulinemia due to excess insulin secretion and/or reduced insulin clearance. If the pancreas can compensate for the insulin resistance, blood sugar levels remain normal; if the pancreas cannot compensate, impaired glucose tolerance and type 2 diabetes develop. There is also some evidence that hyperinsulinemia independently contributes to development of obesity, hypertension, and other cardiovascular risk factors among children (Steinberger et al., 2009).

Effects of Gender, Race, and Other Factors

In adults, development of metabolic syndrome is associated with a number of factors besides obesity and insulin resistance, including older age, smoking, decreased household income, and Mexican-American ethnicity (Park et al., 2003). Similarly, age, gender, race/ethnicity, and family history influence the development of metabolic syndrome in children.

The prevalence of metabolic syndrome in adolescent males is significantly higher than in adolescent females. In studies which examined NHANES data for adolescents aged 12-19 years, prevalence of metabolic syndrome among males was 6.1-9.1%, while prevalence in females was only 2.1-3.7% (Cook, Weitzman, Auinger, Nguyen, & Dietz, 2003; Duncan et al., 2004). In younger children, however, there does not appear to be a gender difference. Multiple studies which examined children under the age of 10 found no significant difference in prevalence of metabolic syndrome between boys and girls (Calcaterra et al., 2008; Pedrosa et al., 2010; Rinaldi et al., 2010).

There also appear to be gender differences in which components of the metabolic syndrome are present. In a 2010 study by Pedrosa and colleagues which examined metabolic

syndrome in obese children aged 7-10 years, hypertension, low HDL, and elevated triglycerides were more common in girls, while boys had a significantly higher waist circumference than girls. In a similar study by Lambert and colleagues (2008) which examined children aged 9, 13, and 16 years, girls had significantly more unfavorable outcomes with regards to total cholesterol, low-density lipoprotein (LDL), HDL, triglycerides, and insulin resistance. Boys, in contrast, had a higher prevalence of impaired fasting glucose.

Racial and ethnic differences in prevalence of metabolic syndrome among children and adolescents are apparent, with prevalence being highest among Hispanics, second-highest among non-Hispanic whites, and lowest among non-Hispanic blacks (Cook et al., 2003; DeFerranti et al., 2004). There are differences in the components of metabolic syndrome which tend to appear in individuals of different racial and ethnic groups. Obesity and insulin resistance tend to be more common in Hispanics and non-Hispanic blacks, and hypertension is most common among black individuals. In contrast, blacks generally have more favorable triglycerides and HDL. These racial and ethnic differences are not well-understood; it is difficult to tell if one racial/ethnic group is truly at higher risk, or if there are different risk thresholds for different groups (Steinberger et al., 2009).

Older children and adolescents are at higher risk for metabolic syndrome than younger children. In a 2008 study by Sen, Kandemir, Alikasifoglu, Gonc, and Ozon which examined children and adolescents aged 2-19 years, subjects with metabolic syndrome were significantly older than those without metabolic syndrome. In another study by Lambert and colleagues (2008) which examined children aged 9, 13, and 16 years, there was an increase in number of metabolic abnormalities with age. Most notably, 16 year old boys were 10 times more likely, and 13 year old boys were 4 times more likely to have 2 or more unfavorable cardiometabolic

characteristics than their 9 year old counterparts. Interestingly, this difference in prevalence with age does not appear to be associated with pubertal stage, as studies examining children between 2 and 19 years did not find any difference in prevalence of metabolic syndrome among children of different Tanner stages (Cook et al., 2003; Rinaldi et al., 2010; Sen et al., 2008).

The evidence regarding associations between parental health history and pediatric metabolic syndrome is mixed. Several studies found no association between parental history of type 2 diabetes or myocardial infarction and presence of pediatric metabolic syndrome (Cook et al., 2003; Sen et al., 2008). Data from the Bogalusa Heart Study, however, showed that offspring of parents with early coronary artery disease are more likely to be overweight as children and to develop an unfavorable cardiovascular risk profile in early adulthood (Bao et al., 1997).

Methods and Procedures

Study Population

Subjects for this study were 222 obese children aged 6-10 years who were seen as new patients in the Lipid Clinic at the Children's Medical Center of Dayton in 2008-2010 for management of obesity and related conditions. Overall, 479 patients met the age and weight parameters described above; 257 of these patients were excluded from this study because they had missing information on any of the following study measures: five hour oral glucose tolerance test, lipid panel, and blood pressure readings.

Data Collection and Measurement Techniques

This study protocol was reviewed and approved for appropriate treatment of human subjects by the Children's Medical Center of Dayton's Institutional Review Board. All data for this study were gathered retrospectively from electronic medical records. Data gathered included age, race/ethnicity, height, weight, and blood pressure from patient's initial clinic visit, as well as results of oral glucose tolerance testing (OGTT), fasting total cholesterol, fasting triglycerides, and high-density lipoprotein cholesterol, which were typically drawn within 14 days following the initial clinic visit.

Measures of Adiposity

Height and weight data were collected at each patient's initial visit to the Lipid Clinic by a registered nurse or trained medical office assistant. Height was measured in meters with patient in bare feet or socks using a ProScale model 150 digital stadiometer (Accurate Technology Inc., Fletcher, NC, USA). Weight was measured in a hospital gown to the nearest 0.1 kilogram on a Detecto Model 6550 folding portable wheelchair scale with Detecto model 758C digital weight indicator (Cardinal Scale Manufacturing Co., Webb City, Missouri, USA).

Body mass index was calculated by dividing the weight of the subject by the height squared (kg/m^2) (Table 1). BMI percentile was then determined using the Centers for Disease Control (CDC) BMI charts for age and gender (National Center for Health Statistics, 2002). Overweight was defined as 85^{th} percentile $\leq$ BMI $< 95^{th}$ percentile, and obesity was defined as BMI $\geq 95^{th}$ percentile as recommended by the Expert Committee on the Assessment, Prevention, and Treatment of Child and Adolescent Overweight and Obesity (Barlow & The Expert Committee, 2007).

In addition to classification into overweight and obese categories, degree of excess weight was described using BMI percentiles and relative BMI (rBMI). Relative BMI is calculated by dividing the subject's actual BMI by the BMI at the 50^{th} percentile for each subject's age and gender using data from the appropriate CDC BMI chart (Table 4). For analyses, the population was stratified into rBMI tertiles.

Table 4
Relative Body Mass Index Formulas

Measurement	Formula
Body Mass Index	Body weight (kg) / height^2 (m^2)
Body Mass Index at 50^{th} Percentile (Females)	$-0.0041x^3 + 0.1529x^2 - 1.2696x + 18.249$ (x = age in years, rounded to the nearest 0.01 year)
Body Mass Index at 50^{th} Percentile (Males)	$-0.0028x^3 + 0.1253x^2 - 1.152x + 18.41$ (x = age in years, rounded to the nearest 0.01 year)
Relative Body Mass Index	(Body Mass Index / Body Mass Index at 50^{th} Percentile)

(National Center for Health Statistics, 2002)

Measures of Blood Pressure

Blood pressure data were collected at each patient's initial visit to the Lipid Clinic by a registered nurse or trained medical office assistant. If more than one blood pressure was collected during the initial visit, the lowest blood pressure was used for this study. Blood pressures were measured with the patient seated using a GE Dinamap Pro 100V2 blood pressure monitor (GE Healthcare, Milwaukee, WI, USA) with appropriately sized cuff, and were interpreted using the age, sex, and height-specific National Heart, Lung, and Blood Institute (NHLBI) blood pressure tables for children and adolescents (National Heart, Lung, and Blood Institute [NHLBI], 2005).

For the purposes of this study, prehypertension was defined as a systolic or diastolic blood pressure greater than or equal to the 90th percentile, but less than the 95th percentile. In addition, patients with systolic blood pressure below the 90th percentile but greater than or equal to 120 mmHg and/or diastolic blood pressure below the 90th percentile but greater than or equal to 80 mmHg were considered to be pre-hypertensive. Stage 1 hypertension was defined as a systolic blood pressure and/or diastolic blood pressure greater than or equal to the 95th percentile for sex, age, and height, but less than the 99th percentile cutoff plus 5 mmHg. Finally, stage 2 hypertension was defined as systolic and/or diastolic blood pressure greater than the 99th percentile cutoff plus 5 mmHg. These definitions are consistent with the NHLBI's definitions, except the NHLBI recommends using the average of three blood pressures which are obtained on different occasions (NHLBI, 2005).

Measures of Glucose Tolerance and Insulin Resistance

Blood glucose and insulin data were collected at the Children's Medical Center of Dayton's short-stay unit within two weeks of the patient's initial clinic visit. Glucose tolerance

was measured following a 12 hour fast using the World Health Organization's oral glucose tolerance test protocol. In this protocol, plasma glucose and insulin are monitored in the fasting state and at one hour intervals following oral administration of anhydrous glucose dissolved in water. Glucose dosing is 1 gram per kilogram of body weight, with a maximum dose of 75 grams (World Health Organization/International Diabetes Federation, 2006). For this study, the American Diabetes Association's definitions for impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes were used. Impaired fasting glucose was defined as fasting glucose greater than or equal to 100 mg/dL; impaired glucose tolerance was defined as a two hour postload glucose of 140 to 199 mg/dL, and type 2 diabetes was defined as a two hour postload glucose of greater than or equal to 200 mg/dL (American Diabetes Association, 2005).

Elevated fasting insulin was defined as fasting insulin greater than or equal to 17 u IU/mL. Degree of insulin resistance was calculated from fasting plasma glucose and insulin levels using the fasting glucose-to-insulin ratio (FGIR) and homeostatic model assessment of insulin resistance (HOMA-IR). FGIR is calculated by dividing fasting glucose in mg/dL by fasting insulin in u IU/mL, while HOMA-IR is calculated by multiplying glucose in mg/dL by insulin in uIU/mL, then dividing the product by 405. FGIR is inversely related to insulin resistance, with FGIR decreasing as insulin resistance increases. Conversely, HOMA-IR increases as insulin resistance increases (Conwell, Trost, Brown, & Batch, 2004).

Measures of Serum Lipids

Blood lipid data were collected at the Children's Medical Center of Dayton's short-stay unit following a 12 hour fast. This lipid panel was drawn within two weeks of the patient's initial clinic visit. For this study, the American Heart Association's guidelines for identification of children and adolescents at high risk for cardiovascular disease was used; high-density

lipoprotein below 35 mg/dL or fasting triglycerides greater than or equal to 150 mg/dL were considered abnormal (Kavey et al., 2003).

Metabolic Syndrome

For this study, metabolic syndrome was defined as BMI greater than or equal to the 85th percentile, plus two or more of the following factors:

- HDL less than 35 mg/dL
- Triglycerides greater than 150 mg/dL
- 2 hour blood glucose on oral glucose tolerance test greater than or equal to 140 mg/dL
- Abnormal blood pressure (Please see definitions of pre-hypertension and hypertension, above.)

Data Analysis

From the data described above, a variety of analyses were performed. Mean values for age, weight, height, BMI, BMI percentile, rBMI, systolic blood pressure, diastolic blood pressure, fasting glucose, two hour glucose, HDL, and total cholesterol were calculated for the entire group and for each rBMI tertile. Additionally, means were calculated for the entire group and each rBMI tertile with the population separated by sex. Two-sample t-tests were used to test for significant differences in means between the sexes, and single-factor ANOVA analyses were performed to test for significant differences in means amongrBMItertiles.

Median values for fasting insulin, FGIR, HOMA-IR, and triglycerides were calculated for the entire group and for each rBMI tertile. Additionally, medians were calculated for the entire group and each rBMI tertile with the population separated by sex. Mann-Whitney tests were

used to test for significant differences in medians between the sexes, Kruskal-Wallis tests were performed to test for significant differences in medians among rBMI tertiles.

Racial distribution was examined for the population as a whole and for each rBMI tertile. Additionally, the distribution was examined for the entire group and each rBMI tertile with the population separated by sex. Chi-square analysis was used to test for significant differences in race distribution between males and females and among rBMI subgroups. Proportions of children with abnormal metabolic parameters were examined for the population as a whole and for each rBMI tertile. Chi-square analysis was used to test for significant differences in prevalence of abnormalities between males and females, and among rBMI subgroups. Finally, the number of metabolic syndrome components and prevalence of metabolic syndrome was calculated for the entire group and for each rBMI tertile. Chi-square analysis was used to test for significant differences between groups.

Results

Demographics and Metabolic Characteristics of the Study Population

Table 5
Demographics and Metabolic Characteristics of Overall Sample, and by Sex

Characteristics	Overall N=222 Mean ± sd, Median (IQR) or n (%)	Males N=88 Mean ± sd, Median (IQR) or n (%)	Females N=134 Mean ± sd, Median (IQR) or n (%)	p-value
Age (y)	9.27 ± 1.33	9.32 ± 1.37	9.24 ± 1.31	0.325†
Race White Black Others	 136 (61.3%) 62 (27.9%) 24 (10.8%)	 62 (70.4%) 21 (23.9%) 5 (5.7%)	 74 (55.2%) 41 (30.6%) 19 (14.2%)	0.040‡
Weight (kg)	62.41 ± 15.06	62.74 ± 13.43	62.18 ± 16.08	0.389†
Height (m)	1.43 ± 0.10	1.42 ± 0.09	1.43 ± 0.11	0.119†
Measures of adiposity				
BMI (kg/m^2)	30.35 ± 5.12	31.09 ± 5.37	29.86 ± 4.90	0.044†
BMI percentile	98.99 ± 1.20	99.22 ± 0.65	98.83 ± 1.43	0.001†
Relative BMI	1.85 ± 0.30	1.90 ± 0.33	1.82 ± 0.28	0.032†
Measures of blood pressure				
SBP (mmHg)	120.47 ± 10.42	120.03 ± 10.69	120.75 ± 10.28	0.309†
DBP (mmHg)	67.17 ± 6.57	67.08 ± 7.17	67.22 ± 6.17	0.439†
Measures of glucose tolerance / insulin resistance				
F GLU (mg/dL)	92.58 ± 7.16	94.27 ± 7.67	91.46 ± 6.59	0.003†
F INS (u IU/mL)	14.90 (9.35)	12.85 (8.00)	17.00 (10.65)	0.001§
2H GLU (mg/dL)	119.99 ± 23.75	120.67 ± 24.63	119.54 ± 23.24	0.366†
FGIR	6.21 (4.49)	7.10 (4.66)	5.40 (3.46)	<0.0001§
HOMA-IR	3.36 (2.18)	2.91 (2.03)	3.88 (2.27)	0.004§
Measures of serum lipids				
TG (mg/dL)	90.50 (71.5)	85.00 (63.25)	92.00 (76.75)	0.221§
HDL (mg/dL)	41.72 ± 9.39	43.48 ± 10.27	40.56 ± 8.61	0.493†
CHOL (mg/dL)	164.66 ± 32.70	169.18 ± 34.10	161.69 ± 31.52	0.389†

Two sample t-tests or Mann-Whitney tests were conducted to test sex differences in continuous variables (e.g., age). Chi-square test was used to examine sex difference in categorical variable (e.g., race).

† 2-sample t-test assuming unequal variances
‡ Chi-square test
§ Mann-Whitney test

Demographic Characteristics

A total of 222 subjects were included in this study, comprising of 39.6% males and 60.4% females. The mean ± sd age of participants was 9.27 ± 1.33 years; there was no

significant difference between the mean age of males and females. Self-described race was grouped into three categories: black, white, and others. Overall, 61.3% of subjects were white, 27.9% were black, and 10.8% were of another race category and were designated as others, or declined to provide this information. Notably, there was a significant difference in the racial distribution of male and female participants on Chi-square analysis (p=0.04). While 70.4% of male participants were white, only 55.2% of female participants were white (Table 5).

Weight and Height

Mean ± sd weight of participants was 62.41 ± 15.06 kilograms, and mean height of participants was 1.43 ± 0.10 meters; there were no significant differences in mean weight or height between male and female participants. However, mean BMI of male participants was significantly higher than the mean BMI of female participants. In addition, rBMI, which adjusts for age and sex, remained significantly higher in males than in females (p=0.032) (Table 5).

Blood Pressure

Table 6
Blood Pressure Profiles in Overall Sample, and by Sex

Blood Pressure Category	Overall N=222 n (%)	Males N=88 n (%)	Females N=134 n (%)	p-value†
Normotensive	82 (36.9%)	35 (39.8%)	47 (35.1%)	0.737
Pre HTN	29 (13.1%)	9 (10.2%)	20 (14.9%)	
Stage 1 HTN	87 (39.2%)	34 (38.6%)	53 (39.6%)	
Stage 2 HTN	24 (10.8%)	10 (11.4%)	14 (10.4%)	

† Chi-square test

Mean systolic blood pressure of the study population was 120.47 ± 10.42 mmHg, and mean diastolic blood pressure was 67.17 ± 6.57 mmHg (Table 5). There were no significant differences in systolic or diastolic blood pressure between males and females. When age, height, and sex-specific cutoffs for hypertension were applied, only 36.9% of subjects were normotensive (Table 6). Overall, 13.1% of subjects had blood pressure categorized as pre-

hypertension, 39.2% had blood pressure categorized as stage 1 hypertension, and 10.8% had blood pressure categorized as stage 2 hypertension. There was no significant difference between males and females with regards to blood pressure categorization.

Table 7
Metabolic Abnormalities in Overall Sample, and by Sex

Characteristics	Overall N=222 n (%)	Males N=88 n (%)	Females N=134 n (%)	p-value†
F GLU ≥ 100 mg/dL	27 (12.2%)	17 (19.3%)	10 (7.5%)	0.008
F INS ≥ 17 u IU/mL	89 (40.1%)	22 (25.0%)	67 (50.0%)	<0.001
Impaired GTT: 140-199 mg/dl @ 2h	26 (11.7%)	12 (13.6%)	14 (10.4%)	0.303
Type 2 DM: ≥ 200 mg/dl @ 2 h	3 (1.4%)	1 (1.1%)	2 (1.5%)	0.654
HDL < 35 mg/dL	44 (19.8%)	13 (14.8%)	31 (23.1%)	0.086
TG >150 mg/dL	41 (18.5%)	14 (15.9%)	27 (20.1%)	0.270

† Chi-square test

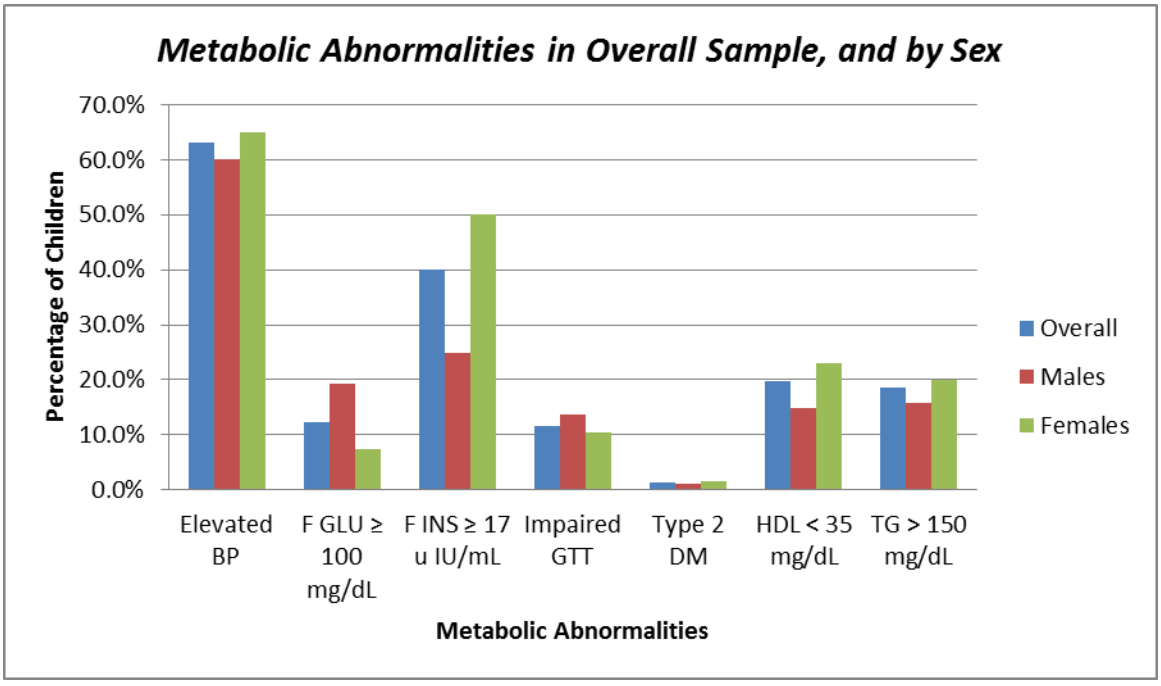

Figure 2. Metabolic Abnormalities in Overall Sample, and by Sex

Glucose levels

Average fasting glucose of the study population was 92.58 ± 7.16 mg/dL (Table 5). Male subjects had significantly higher mean fasting glucose than female subjects, with a mean level of 94.27 ± 7.67 mg/dL for males, and 91.46 ± 6.59 mg/dL for females (p=0.003). Overall, 12.2% of subjects had impaired fasting glucose (fasting glucose of greater than or equal to 100 mg/dL) (Table 7). There was a significant sex difference between the proportion of individuals who had impaired fasting glucose; noted in 19.3% of males versus 7.5% of females (p=0.008). In contrast, there was no significant difference in two hour glucose during glucose tolerance test between males and females. When two hour glucose levels were considered in light of the American Diabetes Association's cutoffs, 11.7% of subjects had impaired glucose tolerance, defined as 2 hour blood glucose between 140 and 199, and 1.4% had type 2 diabetes, defined as a 2 hour blood glucose of 200 and above. There were no significant differences in prevalence of impaired glucose tolerance and type 2 diabetes between males and females (Table 7).

Fasting Insulin and Insulin Sensitivity Indices

The median (IQR) fasting insulin level among all study participants was 14.90 (9.35) u IU/ml (Table 5). There was a significant difference in insulin levels between males and females, with males having a median level of 12.85 (8.00) u IU/ml, and females having a median level of 17.00 (10.65) uIU/mL (p=0.001) (Table 5). Similarly, 50.0% of females had abnormal fasting insulin levels of 17 u IU/mL or greater, while only 25.0% of males had abnormal levels; this difference was highly significant (p<0.001). Overall, 40.1% of subjects had abnormal fasting insulin levels of 17 u IU/mL or greater. As is to be expected considering differences in insulin levels, females were significantly more insulin resistant than males on fasting FGIR and HOMA-IR (Table 5).

Serum Lipids

The median fasting triglyceride level in the study population was 90.50 mg/dL (Table 5), and 18.5% of subjects had abnormal triglyceride levels i.e., greater than 150 mg/dL (Table 7). There were no significant differences between males and females with regards to median triglyceride levels or proportion of individuals with abnormal triglyceride levels. The mean fasting HDL level in the study population was 41.72 ± 9.39 mg/dL (Table 5), and 19.8% of subjects had abnormal HDL levels of less than 35 mg/dL (Table 7). As with triglycerides, there were no significant differences in mean HDL levels or proportion of individuals with abnormal HDL levels between males and females. Finally, the mean ± sd total cholesterol level among study participants was 164.66 ± 32.70 mg/dl; there was no significant difference in mean cholesterol levels between male and female participants (Table 5).

Metabolic Syndrome

Table 8
Distribution of Metabolic Syndrome Components in Overall Sample, and by Sex

Number of Components†	Overall N=222 n (%)	Males N=88 n (%)	Females N=134 n (%)	p-value‡
1	49 (22.1%)	20 (22.7%)	29 (21.6%)	0.469
2	111 (50.0%)	48 (54.5%)	63 (47.0%)	
3	46 (20.7%)	15 (17.0%)	31 (23.1%)	
4	13 (5.9%)	5 (5.7%)	8 (6.0%)	
5	3 (1.3%)	0 (0.0%)	3 (2.2%)	

†Components of metabolic syndrome include BMI≥85th percentile, HDL<35, TG>150, 2H glu≥140, and prehypertension/hypertension
‡Chi-square test

Note: Everyone is qualified for at least one abnormality based on BMI criteria for inclusion in the study.

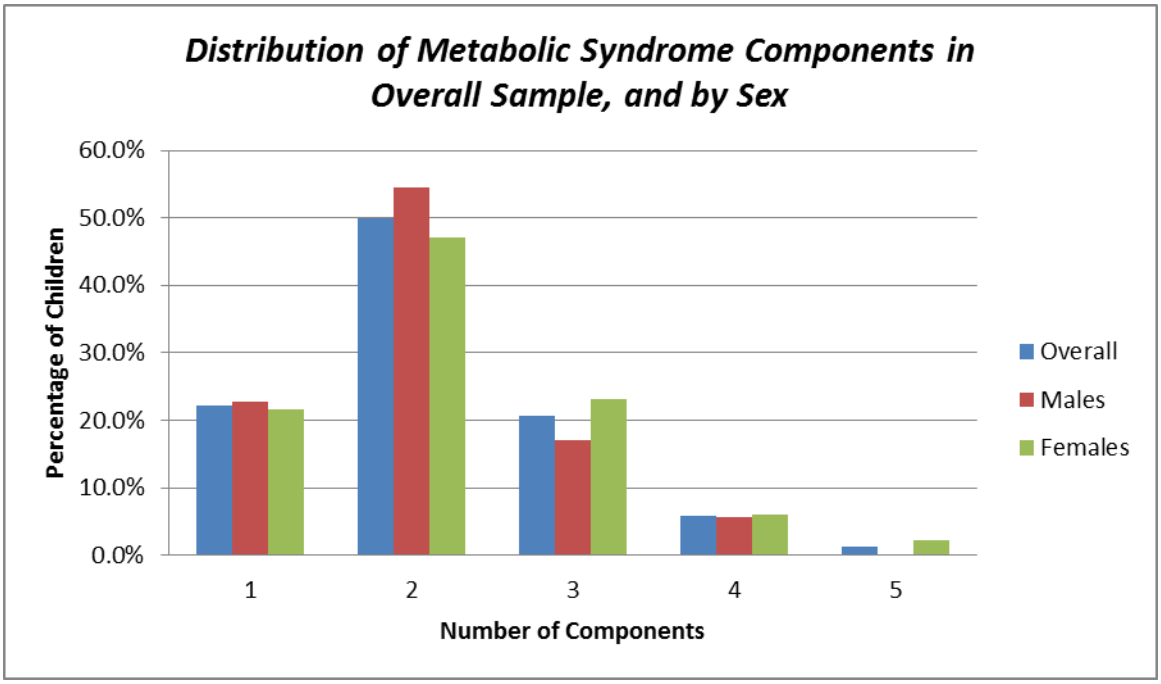

Figure 3. Distribution of Metabolic Syndrome Components in Overall Sample, and by Sex

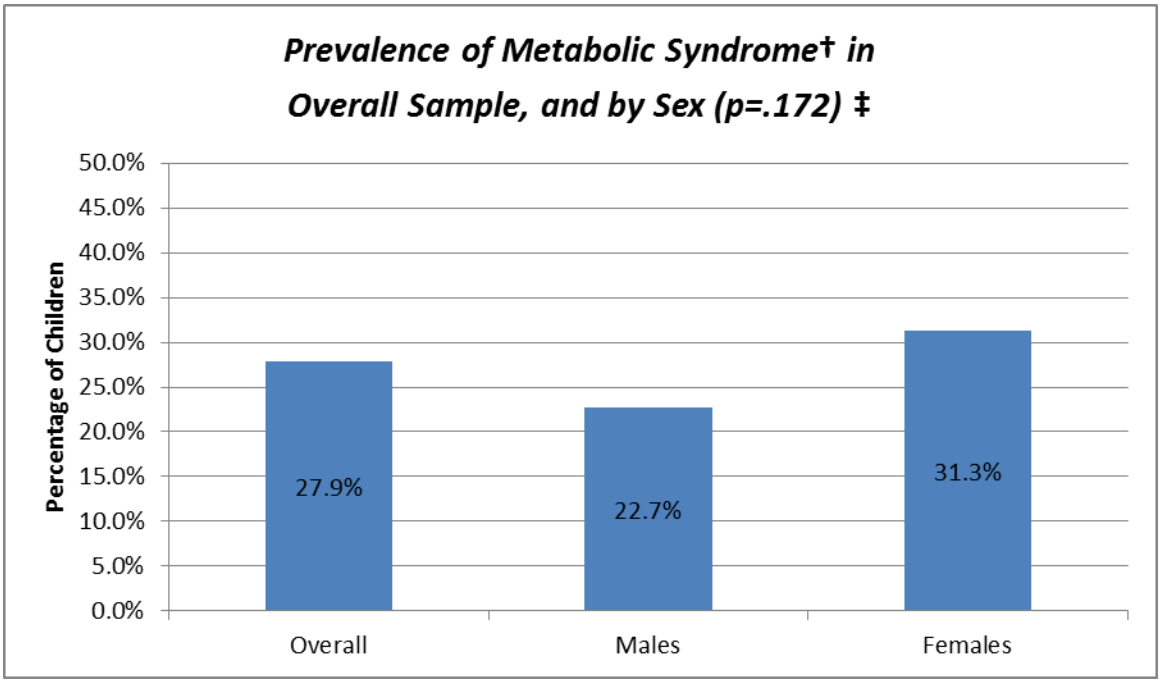

Figure 4. Prevalence of Metabolic Syndrome in Overall Sample, and by Sex

† Metabolic syndrome is defined as BMI≥85th percentile plus 2 or more of the following variables: 1) HDL<35, 2) TG>150, 3) 2H glu≥140, and 4) prehypertension/hypertension
‡Chi-square test
Note: Everyone is qualified for at least one abnormality based on BMI criteria.

Each subject had at least one metabolic syndrome component because BMI greater than or equal to the 85th percentile was one of the inclusion criteria for the study. Only 22.1% of subjects had no abnormalities other than overweight or obesity, 50.0% had one additional abnormality, 20.7% had two additional abnormalities, 5.9% had three additional abnormalities, and 1.3% had every component of the metabolic syndrome (Table 8). There was no significant difference in number of abnormalities between males and females (Table 8). Metabolic abnormalities were clustered into the metabolic syndrome, defined as BMI greater than or equal to the 85th percentile, plus two or more of the following variables: HDL less than 35 mg/dL, triglycerides greater than 150 mg/dL, two hour glucose of 140 mg/dLor greater, and prehypertension/hypertension. Using this definition, 27.9% of study subjects had metabolic syndrome; there was no significant difference in the proportion of males versus females with the syndrome (Figure 4).

Demographics and Metabolic Characteristics by Relative BMI

Study subjects were divided into relative BMI tertiles in order to stratify them by degree of obesity. Subjects in the lowest tertile (tertile one) had relative BMIs greater than 1.24 but less than 1.70, subjects in the middle tertile (tertile two) had relative BMIs of 1.70 to less than 1.93, and subjects in the highest tertile (tertile three) had relative BMIs of 1.93 to 3.15.

Table 9

Demographics and Metabolic Characteristics of Overall Sample by rBMI Category

Characteristics	rBMITertile 1 N=73 Mean ± sd, Median (IQR) or n (%)	rBMITertile 2 N=71 Mean ± sd, Median (IQR) or n (%)	rBMITertile 3 N=78 Mean ± sd, Median (IQR) or n (%)	p-value
Age (y)	9.10 ± 1.41	9.33 ± 1.29	9.38 ± 1.29	0.385†
Sex				
Male	27 (37.0%)	22 (31.0%)	39 (50.0%)	0.051‡
Female	46 (63.0%)	49 (69.0%)	9 (50.0%)	
Race				
White	43 (58.9%)	45 (33.1%)	48 (61.5%)	
Black	22 (30.1%)	19 (26.8%)	21 (26.9%)	0.982‡
Others	8 (11.0%)	7 (9.9%)	9 (11.5%)	
Measures of adiposity				
BMI (kg/m^2)	25.23 ± 2.01	29.6 ± 1.36	35.81 ± 3.74	<0.001†
BMI percentile	97.97 ± 1.63	99.30 ± 0.24	99.67 ± 0.15	<0.001†
Relative BMI	1.55 ± 0.11	1.8 ± 0.06	2.18 ± 0.22	<0.001†
Measures of blood pressure				
SBP (mmHg)	117.47 ± 8.83	121.96 ± 9.85	121.92 ± 11.74	0.010†
DBP (mmHg)	66.81 ± 6.31	68.00 ± 6.18	66.74 ± 7.14	0.433†
Measures of glucose tolerance / insulin resistance				
F GLU (mg/dL)	93.08 ± 7.35	92.61 ± 6.70	92.08 ± 7.43	0.691†
F INS (u IU/mL)	11.6 (9.75)	15.10 (7.60)	18.11 (12.67)	<0.001§
2H GLU (mg/dL)	118.16 ± 24.52	120.52 ± 23.60	121.21 ± 23.36	0.717†
FGIR	7.95 (6.69)	5.91 (2.82)	5.10 (3.54)	<0.001§
HOMA-IR	2.68 (2.43)	3.27 (1.74)	4.11 (2.89)	<0.001§
Measures of serum lipids				
TG (mg/dL)	88.00 (83.00)	94.00 (84.00)	91.50 (59.00)	0.601§
HDL (mg/dL)	42.60 ± 9.89	41.72 ± 9.16	40.88 ± 9.17	0.534†
CHOL (mg/dL)	165.92 ± 40.27	165.17 ± 26.84	163.03 ± 29.88	0.853†

Single-factor ANOVA or Kruskal-Wallis tests were conducted to test differences in continuous variables (e.g., age) among rBMI categories. Chi-square test was used to examine differences in categorical variable (e.g., race) among rBMI categories.

† Single-factor ANOVA
‡ Chi-square test
§Kruskal-Wallis test

Table 10
Metabolic Abnormalities in Overall Sample by rBMI Category

Characteristics	Overall N=222 n (%)	rBMITertile 1 N=73 n (%)	rBMITertile 2 N=71 n (%)	rBMITertile 3 N=78 n (%)	p-value†
Blood pressure Pre HTN S1 HTN S2 HTN	 29 (13.1%) 87 (39.2%) 24 (10.8%)	 11 (15.1%) 24 (32.9%) 5 (6.8%)	 10 (14.1%) 32 (45.1%) 8 (11.3%)	 8 (10.3%) 31 (39.7%) 11 (14.1)	 0.380
F GLU ≥ 100 mg/dL	27 (12.2%)	8 (11.0%)	7 (9.9%)	12 (15.4%)	0.546
F INS ≥ 17 u IU/mL	89 (40.1%)	22 (30.1%)	25 (35.2%)	42 (53.8%)	0.007
Impaired GTT: 140-199 mg/dL @ 2h	26 (11.7%)	5 (6.8%)	11 (15.5%)	10 (12.8%)	0.254
Type 2 DM: ≥ 200 mg/dL@ 2 h	3 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.3%)	0.998
HDL < 35 mg/dL	44 (19.8%)	12 (16.4%)	14 (19.7%)	18 (23.1%)	0.593
TG > 150 mg/dL	41 (18.5%)	13 (17.8%)	17 (23.9%)	11 (14.1)	0.298

† Chi-square test

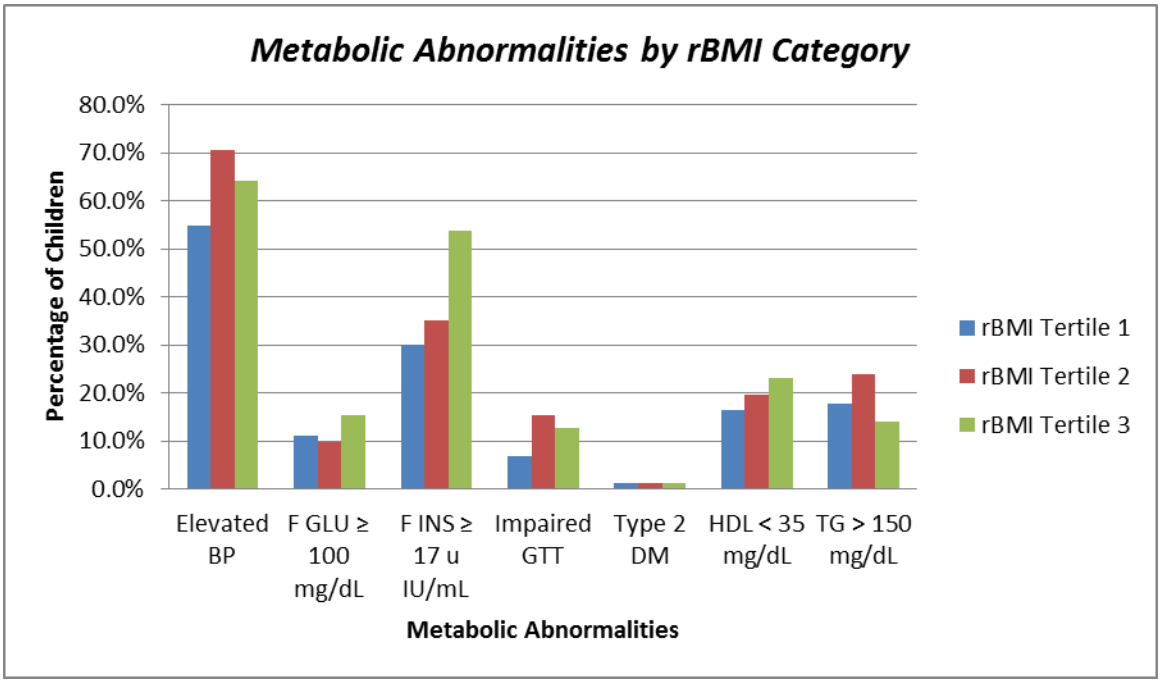

Figure 5. Metabolic Abnormalities by rBMI Category

Table 11
Demographics and Metabolic Characteristics of Males by rBMI Category

Characteristics	rBMITertile 1 N=27 Mean ± sd, Median (IQR) or n (%)	rBMITertile 2 N=22 Mean ± sd, Median (IQR) or n (%)	rBMITertile 3 N=39 Mean ± sd, Median (IQR) or n (%)	p-value
Age (yrs)	9.21 ± 1.47	9.61 ± 1.25	9.23 ± 1.38	0.524†
Race White Black Others	 17 (63.0%) 9 (33.3%) 1 (3.7%)	 17 (77.3%) 2 (9.1%) 3 (13.6%)	 28 (71.8%) 10 (25.6%) 1 (2.6%)	0.150‡
Measures of adiposity				
BMI (kg/m^2)	25.58 ± 1.33	29.94 ± 1.29	35.54 ± 4.61	<0.001†
BMI percentile	98.56 ± 0.77	99.31 ± 0.24	99.63 ± 0.18	<0.001†
Relative BMI	1.57 ± 0.07	1.82 ± 0.07	2.17 ± 0.28	<0.001†
Measures of blood pressure				
SBP (mmHg)	116.89 ± 8.92	112.09 ± 10.57	121.05 ± 11.61	0.174†
DBP (mmHg)	67.52 ± 6.85	67.86 ± 5.69	66.33 ± 8.16	0.680†
Measures of glucose tolerance / insulin resistance				
F GLU (mg/dL)	94.22 ± 9.28	94.41 ± 5.44	94.23 ± 7.12	0.995†
F INS (u IU/mL)	10.40 (4.67)	13.40 (6.97)	14.20 (11.80)	0.006§
2H GLU (mg/dL)	119.11 ± 17.97	122.91 ± 27.58	120.49 ± 27.26	0.867†
FGIR	9.41 (4.55)	6.90 (5.29)	6.21 (4.75)	0.005§
HOMA-IR	2.37 (1.49)	2.97 (1.62)	3.45 (2.40)	0.007§
Measures of serum lipids				
TG (mg/dL)	67.00 (86.00)	104.00 (81.25)	72.00 (60.00)	0.278§
HDL (mg/dL)	44.89 ± 10.91	43.18 ± 10.80	42.67 ± 9.67	0.685†
CHOL (mg/dL)	177.41 ± 45.15	167.14 ± 31.03	164.64 ± 25.76	0.314†

Single-factor ANOVA or Kruskal-Wallis tests were conducted to test differences in continuous variables (e.g., age) among rBMI categories. Chi-square test was used to examine differences in categorical variable (e.g., race) among rBMI categories.

† Single-factor ANOVA
‡ Chi-square test
§Kruskal-Wallis test

Table 12
Metabolic Abnormalities in Males by rBMI Category

Characteristics	Overall N=88 n (%)	rBMITertile 1 N=27 n (%)	rBMITertile 2 N=22 n (%)	rBMITertile 3 N=39 n (%)	p-value†
Blood pressure					
Pre HTN	9 (10.2%)	4 (14.8%)	2 (9.1%)	3 (7.7%)	0.672
S1 HTN	34 (38.6%)	8 (29.6%)	11 (50.0%)	15 (38.6%)	
S2 HTN	10 (11.4%)	2 (7.4%)	3 (13.6%)	10 (11.4%)	
F GLU ≥ 100 mg/dL	17 (19.3%)	4 (14.8%)	3 (13.6%)	10 (25.6%)	0.405
F INS ≥ 17 u IU/mL	22 (25.0%)	3 (11.1%)	4 (18.2%)	15 (38.5%)	0.029
Impaired GTT: 140-199 mg/dL @ 2h	12 (13.6%)	2 (7.4%)	6 (27.3%)	4 (10.3%)	0.093
Type 2 DM: ≥ 200 mg/dL @ 2 h	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	-
HDL < 35 mg/dL	13 (14.8%)	2 (7.4%)	4 (18.2%)	7 (17.9%)	0.432
TG > 150 mg/dL	14 (15.9%)	4 (14.8%)	5 (22.7%)	5 (12.8%)	0.587

† Chi-square test

Table 13
Demographics and Metabolic Characteristics of Females by rBMI Category

Characteristics	rBMITertile 1 N=46 Mean ± sd, Median (IQR) or n (%)	rBMITertile 2 N=49 Mean ± sd, Median (IQR) or n (%)	rBMITertile 3 N=39 Mean ± sd, Median (IQR) or n (%)	p-value
Age (yrs)	9.03 ± 1.39	9.20 ± 1.30	9.53 ± 1.19	0.202†
Race				
White	26 (56.5%)	28 (57.1%)	20 (51.3%)	0.563‡
Black	13 (28.3%)	17 (34.7%)	11 (28.2%)	
Others	7 (15.2%)	4 (8.2%)	8 (20.5%)	
Measures of adiposity				
BMI (kg/m^2)	25.02 ± 2.30	29.45 ± 1.38	36.09 ± 2.64	<0.001†
BMI percentile	97.62 ± 1.89	99.29 ± 0.24	99.70 ± 0.09	<0.001†
Relative BMI	1.53 ± 0.13	1.80 ± 0.06	2.18 ± 0.14	<0.001†
Measures of blood pressure				
SBP (mmHg)	117.80 ± 8.87	121.90 ± 9.63	122.79 ± 11.96	0.050†
DBP (mmHg)	66.39 ± 6.02	68.06 ± 6.44	67.15 ± 6.03	0.421†
Measures of glucose tolerance / insulin resistance				
F GLU (mg/dL)	92.41 ± 5.95	91.80 ± 7.10	89.92 ± 6.53	0.202†
F INS (u IU/mL)	13.30 (12.41)	16.00 (7.55)	20.80 (11.49)	0.002§
2H GLU (mg/dL)	117.61 ± 27.83	119.45 ± 21.81	121.92 ± 19.01	0.698†
FGIR	6.75 (8.05)	5.61 (2.37)	4.33 (2.87)	0.001§
HOMA-IR	3.09 (2.78)	3.64 (1.99)	4.41 (2.70)	0.005§
Measures of serum lipids				
TG (mg/dL)	91.00 (83.50)	88.00 (87.00)	94.00 (55.00)	0.989§
HDL (mg/dL)	41.26 ± 9.09	41.26 ± 9.09	39.10 ± 8.39	0.456†
CHOL (mg/dL)	159.17 ± 35.94	159.17 ± 35.94	161.41 ± 33.77	0.733†

Single-factor ANOVA or Kruskal-Wallis tests were conducted to test differences in continuous variables (e.g., age) among rBMI categories. Chi-square test was used to examine differences in categorical variable (e.g., race) among rBMI categories. † Single-factor ANOVA; ‡ Chi-square test; § Kruskal-Wallis test

Table 14
Metabolic Abnormalities in Females by rBMI Category

Characteristics	Overall N=134 n (%)	rBMITertile 1 N=46 n (%)	rBMITertile 2 N=49 n (%)	rBMITertile 3 N=39 n (%)	p-value†
Blood pressure					
Pre HTN	20 (14.9%)	7 (15.2%)	8 (16.3%)	5 (12.8%)	0.730
S1 HTN	53 (39.6%)	16 (34.8%)	21 (42.9%)	16 (41.0%)	
S2 HTN	14 (10.4%)	3 (6.5%)	5 (10.2%)	6 (15.4%)	
F GLU ≥ 100 mg/dL	10 (7.5%)	4 (8.7%)	4 (8.2%)	2 (5.1%)	0.801
F INS ≥ 17 u IU/mL	67 (50.0%)	19 (41.3%)	21 (42.95)	27 (69.0%)	0.017
Impaired GTT: 140-199 mg/dL @ 2h	14 (10.4%)	3 (6.5%)	5 (10.2%)	6 (15.4%)	0.411
Type 2 DM: ≥ 200 mg/dL @ 2 h	2 (1.5%)	1 (2.2%)	1 (2.0%)	0 (0.0%)	-
HDL < 35 mg/dL	31 (23.1%)	10 (21.7%)	10 (20.4%)	11 (28.2%)	0.664
TG > 150 mg/dL	27 (20.1%)	9 (19.6%)	12 (24.5%)	6 (15.4%)	0.567

† Chi-square test

Demographic Characteristics

There was no significant difference among rBMI tertiles with regards to age. The mean ± sd ages of subjects were 9.10 ± 1.41 years, 9.33 ± 1.29 years, and 9.38 ± 1.29 years in tertiles one, two, and three, respectively (Table 9). When subjects were divided into male and female groups, mean ages were not significantly different across tertiles (Tables 11 and 13). In the overall sample, there was no significant difference in sex distribution among rBMI tertiles (Table 9). Similarly, there was no significant difference in racial distribution among rBMI tertiles, both when the population was considered as a whole, and when it was divided by sex (Tables 9, 11, and 13).

Blood Pressure

There were significant differences in systolic blood pressure among rBMI tertiles. In rBMI tertile one, mean systolic blood pressure was 117.47 ± 8.83 mmHg; in rBMI tertile two, mean systolic blood pressure was 121.96 ± 9.85 mmHg; in rBMI tertile three, mean systolic blood pressure was 121.92 ± 11.74 mmHg. Single-factor ANOVA suggests that these means are

significantly different at p=0.01(Table 9). When subjects were divided by sex, there was no significant difference in systolic blood pressure among rBMI tertiles in males (Table 11). In females, however, differences in systolic blood pressure were significant at p=0.05 (Table 13). There were no significant differences in mean diastolic blood pressure among rBMI tertiles, both when the population was considered as a whole, and when it was divided by sex (Tables 9, 11, and 13).

When age, height, and sex-specific cutoffs for blood pressure were applied, there was no significant difference in the proportion of subjects with prehypertension, stage 1 hypertension, and stage 2 hypertension among rBMI tertiles (Table 10). When subjects were divided into male and female groups, there was still no significant difference in the frequency of prehypertension, stage 1 hypertension, and stage 2 hypertension among the rBMI tertiles (Tables 12 and 14).

Glucose Levels

Overall, there was no significant difference in fasting glucose levels among the rBMI tertiles (Table 9). When subjects were divided into male and female groups, there was still no significant difference in mean fasting glucose among rBMI tertiles (Tables 11 and 13). When the American Diabetes Association cutoff for impaired fasting glucose was applied, there was no significant difference in prevalence among rBMI tertiles for the whole population, for males, or for females (Tables 10, 12, and 14).

There was no significant difference in mean two hour glucose on glucose tolerance test among rBMI tertiles for the study population as a whole, for males, or for females (Tables 9, 11, and 13). Similarly, there were no significant differences in prevalence of impaired glucose tolerance or type 2 diabetes among rBMI tertiles (Tables 10, 12, and 14).

Fasting Insulin and Insulin Sensitivity Indices

There were highly significant differences in insulin levels among rBMI tertiles. Overall, the median fasting insulin was 11.60 u IU/mL in tertile one, 15.10 u IU/mL in tertile two, and 18.11 u IU/mLin tertile three; these medians are significantly different at $p<0.001$ using the Kruskal-Wallis test (Table 9). Differences in median fasting insulin among rBMI tertiles remained significant when the population was split by sex, with $p=0.006$ for males and $p=0.002$ for females (Tables 11 and 13).

Similarly, there was a significant difference in the proportion of subjects with abnormal fasting insulin of greater than or equal to 17 u IU/ml among rBMI tertiles ($p=0.007$). In tertile one, 30.1% of subjects had abnormal fasting insulin; in tertile two, 35.2% of subjects had abnormal fasting insulin; in tertile three, 53.8% of subjects had abnormal fasting insulin (Table 10). Differences in the proportion of subjects with abnormal fasting insulin among rBMI tertiles remained significant when the population was split by sex (Tables 12 and 14).

As is to be expected considering differences in insulin levels, there were significant differences in FGIR and HOMA-IR among rBMI tertiles. The median FGIR in tertile one was 7.95, the median FGIR in tertile two was 5.91, and the median FGIR in tertile three was 5.10; these values are significantly different ($p<0.001$). Similarly, the median HOMA-IR value was 2.68 in tertile one, 3.27 in tertile two, and 4.11 in tertile three ($p<0.001$) (Table 9). Differences in median FGIR and HOMA-IR among rBMI tertiles remained significant when the population was split by sex (Tables 11 and 13).

Serum Lipids

There were no significant differences in median triglyceride levels, mean HDL levels, or mean total cholesterol levels among rBMI tertiles; this was true for the entire study population

and when the population was separated by sex (Tables 9, 11, and 13). Similarly, when HDL and triglyceride levels were considered using the American Diabetes Association's cutoffs, there were no significant differences in prevalence of low HDL or high triglycerides among rBMI tertiles (Tables 10, 12, and 14).

Metabolic Syndrome

Table 15
Distribution of Metabolic Syndrome Components in Overall Sample, and rBMI Category

Number of Components†	Overall N=222 n (%)	rBMITertile 1 N=73 n (%)	rBMITertile 2 N=71 n (%)	rBMITertile 3 N=78 n (%)	p-value‡
1	49 (22.1%)	18 (24.7%)	13 (18.3%)	18 (23.1%)	0.217
2	111 (50.0%)	42 (57.5%)	34 (47.9%)	35 (44.9%)	
3	46 (20.7%)	11 (15.1%)	15 (21.1%)	20 (25.6%)	
4	13 (5.9%)	1 (1.4%)	7 (9.9%)	5 (6.4%)	
5	3 (1.4%)	1 (1.4%)	2 (2.8%)	0 (0.0%)	

†Components of metabolic syndrome include BMI≥85th percentile, HDL<35, TG>150, 2H glu≥140, and prehypertension/hypertension
‡ Chi-Square test
Note: Everyone is qualified for at least one abnormality based on BMI criteria for inclusion in the study.

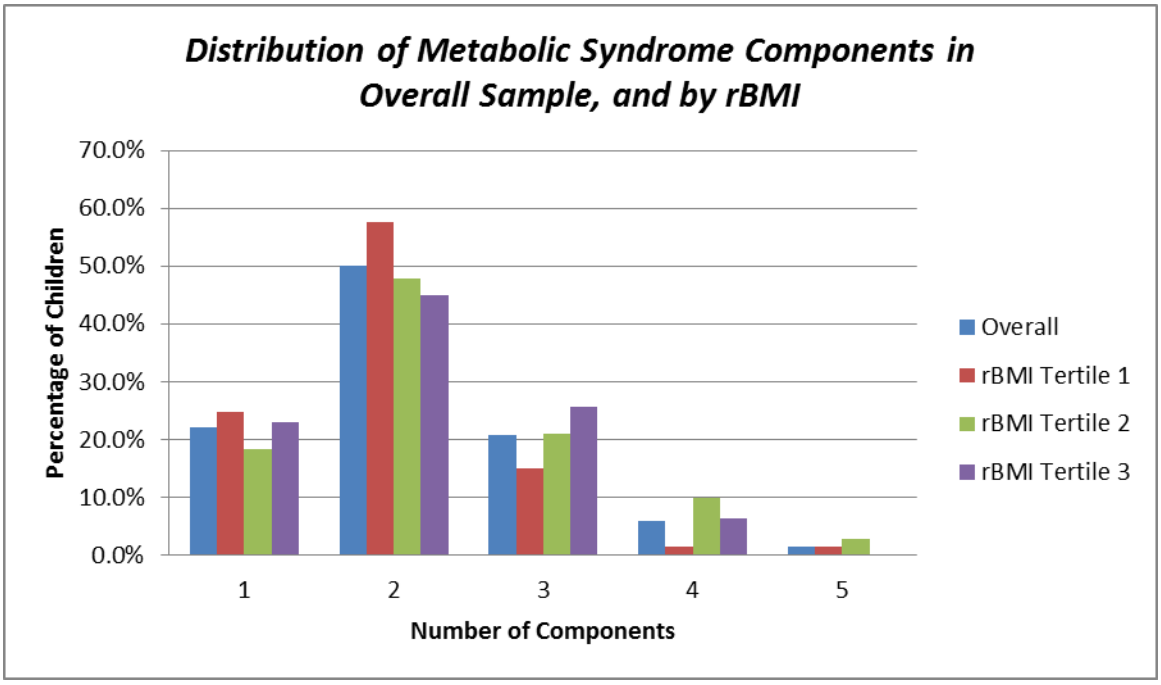

Figure 6. Distribution of Metabolic Syndrome Components in Overall Sample, and by rBMI

Table 16
Prevalence of Metabolic Syndrome by rBMI Category

Metabolic syndrome†	Overall n (%)	rBMITertile 1 n (%)	rBMITertile 2 n (%)	rBMITertile 3 n (%)	p-value‡
Overall Sample	N=222	N=73	N=71	N=78	
	62 (27.9%)	13 (17.8%)	24 (33.8%)	25 (32.1%)	0.061
Males	N=88	N=27	N=22	N=39	
	20 (22.7%)	3 (11.1%)	8 (36.4%)	9 (23.1%)	0.110
Females	N=134	N=46	N=49	N=39	
	42 (31.3%)	10 (21.7%)	16 (32.7%)	16 (41.0%)	0.156

Metabolic syndrome is defined as BMI≥85th percentile plus 2 or more of the following variables: 1) HDL<35, 2) TG>150, 3) 2H glu≥140, and 4) prehypertension/hypertension
‡Chi-square test
Note: Everyone is qualified for at least one abnormality based on BMI criteria.

Metabolic abnormalities were clustered into the metabolic syndrome, defined as BMI greater than or equal to the 85th percentile, plus two or more of the following variables: HDL less than 35 mg/dL, triglycerides greater than 150 mg/dL, two hour glucose of 140 mg/dL or greater, and prehypertension/hypertension. Using this definition, 17.8% of subjects in rBMI tertile one, 33.8% in rBMI tertile two, and 32.1% in rBMI tertile three had metabolic syndrome. These proportions were not significantly different when tested using chi-square analysis (Table 16).

Discussion

Prevalence and Determinants of Metabolic Syndrome among Overweight and Obese Children

The prevalence of metabolic syndrome among obese children and adolescents has varied greatly among studies, likely due to differences in study populations and the definitions used for metabolic syndrome. The overall prevalence of metabolic syndrome in this study was 27.9%. This is slightly higher than a prevalence of 19.1% among obese children in Pedrosa and colleagues' (2010) examination of metabolic syndrome in 7-9 year old Portuguese schoolchildren. This may be due to dissimilarity in characteristics of the population from which subjects were drawn; our study is based on patients who were referred to a hospital-based clinic, while Pedrosa's study recruited subjects from public schools.

Conversely, prevalence of metabolic syndrome found in this study population was lower than in many other studies. Sen et al.'s 2008 study, which examined obese children aged 2-19 years referred to a university clinic, found a prevalence of 41.8%. Additionally, Weiss's 2004 study of obese children aged 2-19 years found a prevalence of 38.7% to 49.7 % depending on severity of obesity. De Ferranti and colleagues (2004), who examined adolescents aged 12 to 19 years, found a prevalence of metabolic syndrome of 31.2% among overweight and obese children. It is possible that the prevalence in this study is lower because the target age range in this study is lower (6-10 years) than in aforementioned studies, and multiple studies have found that older children are at higher risk for metabolic syndrome than younger children (Lambert et al., 2008, Sen et al., 2008). In this study, for example, mean age of participants was 9.27 years, while the Sen and Weiss studies both had subjects with a mean age of 12.1 years. Similarly, this

study examined children aged 6 to 10 years, while DeFerranti examined adolescents aged 12 to 19 years.

In contrast to studies by Calcaterra and colleagues (2008) and Sen and colleagues (2008), this study did not find any significant difference in prevalence of metabolic syndrome based on degree of obesity. Similarly, Calcaterra and Sen found significant differences in the number of metabolic abnormalities per individual based on severity of obesity, while this study did not. In this study, there was no significant difference in prevalence of metabolic syndrome between boys and girls, which is consistent with several other studies which examined children under the age of 10 years (Calcaterra et al., 2008; Pedrosa et al., 2010; Rinaldi et al., 2010).

Prevalence of Individual Metabolic Abnormalities among Overweight and Obese Children

Hypertension

Mean systolic blood pressure of 120.47 mmHg in this study was similar to mean systolic blood pressure of overweight and obese subjects in several other studies. For example, Sen and colleagues (2008) found a mean of 115.8 mmHg, Calcaterra and colleagues (2008) found a mean of 116.5 mmHg, and Weiss and colleagues (2004) found a mean of 121.9 mmHg. In this study, mean systolic blood pressure was significantly different among rBMItertiles. In other studies, blood pressure increased incrementally with increasing BMI z-score (Weiss et al., 2004; Calcaterra et al., 2008). While in this study, mean systolic blood pressure varied among rBMI tertiles, prevalence of abnormal blood pressure did not vary significantly with degree of obesity. This is in contrast to Sen and colleagues' 2008 study, which found that the prevalence of hypertension was significantly different ($p=0.001$) among groups of children stratified by BMI z-score.

The prevalence of abnormal blood pressure among subjects in this study was alarmingly high. When age, height, and sex-specific cutoffs for hypertension were applied, 13.1% of subjects had blood pressure readings consistent with pre-hypertension, 39.2% had readings consistent with stage 1 hypertension, and 10.8% had readings consistent with stage 2 hypertension. This leaves only 36.9% of subjects who were normotensive. Pedrosa and colleagues (2010) had similar results, finding prehypertension or hypertension in almost 70% of overweight and obese children aged 7-9 years. Other studies had a much lower prevalence of abnormal blood pressure levels. For example, Cook, Weitzman, Auinger, Nguyen, and Dietz's 2003 study of adolescents aged 12 to 19 found that only 8.6% of overweight and 11.2% of obese subjects had prehypertension or hypertension. Similarly, Lambert and colleagues (2008) found that 28.8% of overweight and 39.6% of obese subjects had prehypertension or hypertension.

The high rate of hypertension in this study may be partly due to methodological error; both Cook and Lambert took the mean of multiple blood pressure readings, while most subjects in this study had their blood pressure measured only one time. Additionally, elevated blood pressure may be in part to white coat hypertension, which is when patients exhibit elevated blood pressure in clinical settings but not in other settings. Studies of white coat hypertension in children have reported prevalence of 44-88%, depending on the thresholds used for hypertension (Sorof, 2000). While white coat hypertension may be a contributor to the high prevalence of hypertension in this study, it does not explain the significant difference in systolic blood pressure among rBMItertiles.

Impaired Fasting Glucose, Impaired Glucose Tolerance, and Type 2 DM

In this study, 12.2% of subjects had impaired fasting glucose, defined as fasting glucose greater than or equal to 100 mg/dL. Mean fasting glucose levels and the prevalence of impaired

fasting glucose were significantly higher in males than in females in this study; similar findings were apparent in other studies (Duncan et al., 2004; Lambert et al., 2008). In this study, 11.7% of subjects had impaired glucose tolerance, and 1.4% of subjects had type 2 diabetes. This is quite different from Sen and colleagues' 2008 study, which found a 6.0% prevalence of impaired glucose tolerance, and 2.6% prevalence of type 2 diabetes in obese children aged 2-19 years.

There were no significant differences in mean fasting glucose or mean 2 hour glucose among rBMI tertiles in this study. This is in contrast to Calcaterra and colleagues' study (2008) which found significant differences in mean fasting glucose and mean 2 hour glucose among overweight, moderately obese, and severely obese subjects. In this study, there were also no significant differences in the proportion of subjects who had impaired fasting glucose or impaired glucose tolerance among rBMI tertiles. Weiss and colleagues (2004), however, found significant differences in the prevalence of impaired glucose tolerance among subjects who were overweight, moderately obese, and severely obese.

Fasting Insulin and Insulin Sensitivity Indices

In this study, median fasting insulin for the entire population was 14.90 u IU/mL; in Calcaterra and colleagues' 2008 study and in Sen and colleagues' 2008 study, mean fasting insulin levels were 13.6 u IU/mL and 16.4 u IU/mL, respectively. Fasting insulin in this study was significantly different among rBMI tertiles, with insulin levels rising with increasing severity of obesity; the same trend was observed in the Sen and Calcaterra studies.

Overall, 40.1% of subjects had elevated fasting insulin using the cutoff of insulin greater than or equal to 17 u IU/mL. The true percentage of subjects with fasting hyperinsulinemia was likely much higher because the fasting insulin cutoff for prepubertal children is greater than or equal to 13 u IU/mL (Jean et al., 2009; Arslanian, Suprasongsin, & Janosky, 1997). Because

pubertal staging was not available for study subjects, a conservative choice was made to use the 17 u IU/mL cutoff, but it is likely that many of the subjects, particularly male, were still prepubertal. The proportion of subjects with abnormal fasting insulin was significantly different among rBMI tertiles, with the prevalence of abnormal fasting insulin rising with increasing severity of obesity; this trend was seen in several other studies (Weiss et al., 2004; Lambert et al., 2008).

As is to be expected considering differences in insulin levels, there was a significant difference in FGIR among rBMI tertiles. FGIR is inversely related to insulin resistance, with FGIR decreasing as insulin resistance increases. There was also a significant difference in HOMA-IR among rBMI tertiles. HOMA-IR increases as insulin resistance increases. These results are consistent with the literature; in a 2002 study examining the relationship between adiposity and insulin resistance, body fat accounted for 55% of the variance in insulin sensitivity after adjusting for age, gender, race, and pubertal stage (Caprio, 2002). In another study by Velasquez-Meiyer and colleagues (2008), two different indices of insulin sensitivity decreased significantly as the severity of overweight increased.

This study suggests that the prevalence of insulin resistance is higher in females than in males. Median fasting insulin was significantly higher for females than for males, and the proportion of females with elevated fasting insulin was twice that of males. Similarly, median FGIR was lower for females than for males, and median HOMA-IR was higher for females than males. This is consistent with the literature. In one study of healthy five year old children, girls were 33% more insulin resistant than boys after adjusting for body fat and physical activity (Murphy et al., 2004). Several studies suggest that the relationship between gender and insulin

resistance continues into adolescence, with girls having a higher prevalence of insulin resistance independent of pubertal stage and adiposity (Travers, Jeffers, Bloch, Hill, & Eckel, 1995).

Dyslipidemia

In this study, the median triglyceride level of subjects was 90.50 mg/dL, and 18.5% of subjects had abnormal triglyceride levels of greater than 150 mg/dL. This is similar to a 2008 study by Lambert and colleagues in which 17.5% of subjects had triglycerides greater than 150 mg/dL. Several studies reviewed used a less stringent definition of elevated triglycerides of greater than or equal to 110 mg/dL; these studies found a slightly higher prevalence. For example, Cook and colleagues (2003) found a prevalence of 23.4% among obese adolescents, and Duncan, Li, and Zhou (2004) found a prevalence of 23.2% among obese adolescents.

This study found no significant differences in median triglyceride levels or the prevalence of elevated triglycerides between the sexes; Pedrosa et al. (2010) had similar findings in a study of 7-9 year old children. In contrast, a study by Lambert and colleagues (2008) found significantly higher triglyceride levels in overweight and obese females than in overweight and obese males. Additionally, this study found no significant differences in median triglyceride levels or the prevalence of elevated triglycerides among rBMItertiles; however, several studies found that mean triglyceride levels were significantly higher in more obese children (Weiss et al., 2004; Calcaterra et al., 2008).

In this study, 19.8% of subjects had abnormal HDL levels of less than 35 mg/dL, which is lower than in several other studies. Lambert and colleagues (2008) found a prevalence of 25.7% using the same cutoff as was used in this study. Duncan and colleagues (2004) and Cook and colleagues (2003) found prevalences of 23.4% and 23.3%, respectively, using a less stringent cutoff of less than or equal to 40 mg/dL. This study found no significant differences in

mean HDL levels or the prevalence of low HDL among rBMItertiles; however, several studies found that mean HDL levels were lower higher in more obese children (Weiss et al., 2004; Calcaterra et al., 2008).

Limitations

This study has several limitations. Because subjects were selected from a referral-based clinic, and because only children with an extensive biochemical workup could be included in the study, this study may not accurately describe the prevalence of metabolic abnormalities in obese children. Additionally, because physicians in the clinic chose what biochemical tests to perform based on physical examination, it is possible that subjects with the appropriate labs to be included in the study all had similar risk profiles; this may explain why there was no apparent effect of relative obesity on prevalence of metabolic abnormalities.

This study, like all studies which examine the metabolic syndrome in children, is limited by the lack of a consistent, accepted definition for the condition in pediatrics. This lack of standardized parameters makes it difficult to compare the prevalence of metabolic syndrome across studies. In addition, this study fails to consider factors such as birth history, family history, lifestyle, and pubertal stage, which may affect the development of metabolic abnormalities. Because of its cross-sectional design, this study does not allow for causal inference; instead, it simply describes a correlation between relative obesity and prevalence of metabolic risk factors. Finally, each risk factor with the exception of obesity was defined by a singular cutoff point, which may not thoroughly describe the continuum of risk.

Implications and Recommendations

The Need for Aggressive Screening

Current recommendations for physical and biochemical assessment of overweight and obese children are outlined in the Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity (Barlow & The Expert Committee, 2007). The results of this study suggest that the Expert Committee guidelines are insufficient for school-age children; more aggressive screening of overweight and obese children aged 6 to 10 years is warranted because the prevalence of such abnormalities is significant in this population.

The 63.1% prevalence of pre-hypertension and hypertension in this study population reinforces the Expert Committee recommendation to check blood pressure at all health supervision visits. However, most of the Expert Committee's recommendations are not aggressive enough. The Expert Committee's current recommendation is to obtain a fasting lipid profile in all overweight and obese children over the age of 10 years. Almost 20% of this study's 6-10 year-old subjects had elevated triglycerides, and almost 20% had low HDL, suggesting that children under the age of 10 years are at risk of dyslipidemia and should have a fasting lipid panel drawn upon initial assessment. Similarly, the Expert Committee recommends checking fasting glucose in all obese children over the age of 10 years. This recommendation may be insufficient as 12.2% of the 6-10 year old children in this study had impaired fasting glucose.

The Expert Committee does not recommend oral glucose tolerance tests or fasting insulin tests in overweight and obese children; however, this study suggests that both tests may be useful assessment tools in this population. Overall, 13% of children in this study had abnormal blood glucose levels at the 2 hour point on OGTT, and a substantial proportion of those children had

normal fasting glucose levels. Additionally, 40.1% of study subjects had elevated fasting insulin levels, which never would have been found had the Expert Committee's recommendations been followed. Elevated fasting insulin levels suggest insulin resistance, which has been implicated in the pathophysiology of type 2 diabetes, non-alcoholic fatty liver disease, and cardiovascular disease (Steinberger et al., 2009).

The Importance of Relative Obesity in School-Age Children

Multiple studies have suggested that prevalence of metabolic syndrome, prevalence of individual metabolic abnormalities, and the number of abnormalities per individual increase with higher levels of adiposity (Weiss et al., 2004; Lambert et al., 2008, Calcaterra et al., 2008). In this study, however, the only differences noted among rBMItertiles were in systolic blood pressure, fasting insulin, and insulin sensitivity indices. This may be explained by age differences in study populations, because the participants in this study were much younger than the populations of the Weiss, Lambert, and Calcaterra studies, which included adolescents up to the ages of 16 to 20 years. The one study which examined only children aged 7 to 9 years had similar findings to this study, with only systolic blood pressure showing a significant difference among children of different degrees of overweight/obesity (Pedrosa et al., 2010). As a result, we may hypothesize that degree of obesity has less of an effect on development of metabolic abnormalities among younger children than among older children and adolescents.

The Need for Aggressive Intervention

Metabolic risk factors in early in childhood may lead to chronic diseases later in childhood, including type 2 diabetes, non-alcoholic fatty liver disease, and early signs of cardiovascular disease such as left ventricular hypertrophy and thickening of the artery walls (Calcaterra et al., 2008; Kapiotis et al., 2006; Chinali et al., 2008). Additionally, childhood

metabolic syndrome tracks into adulthood and is a risk factor for adult disease (Magnussen et al., 2010; Morrison et al., 2007). In fact, development of risk factors early in life may result in earlier onset of cardiovascular disease and poorer outcomes due to longer duration of exposure (Halpern et al., 2010).

This study suggests that 6-10 year old obese children who are referred for treatment are a population at high risk of morbidity, with 27.9% of subjects in this study having the metabolic syndrome phenotype. Fortunately, aggressive intervention including dietary counseling, structured physical activity, behavioral/family counseling, and even medication or bariatric surgery, may reduce the risk of illness in obese children. Childhood is an optimal time to shape healthy behaviors; additionally, the potential damage to the cardiovascular system in childhood is reversible. When at-risk children are identified early and treated aggressively, the threat of future disease can be mitigated (Battista et al., 2009).

Areas for Further Study

There are a number of additional analyses which could be performed on the dataset from this study. This study primarily compared continuous or categorical metabolic parameters to categories of relative obesity; it would be interesting to see if there are significant correlations between continuous metabolic parameters and rBMI as a continuous variable. In addition, one could quantify a relationship between categorical metabolic parameters and rBMI as a continuous variable using logistic regression. Finally, it would be very interesting to compare average values of metabolic parameters between subjects with and without the metabolic syndrome. This may provide some insights into which metabolic parameters, besides obesity, are major contributing factors to the metabolic syndrome in obese young children.

Conclusion

The presence of metabolic abnormalities in children greatly increases the risk for medical problems such as type 2 diabetes and cardiovascular disease. The results of this study suggest that 6-10 year old obese children who are referred for treatment are a population at high risk of morbidity; 77.9% of subjects had at least one metabolic abnormality in addition to obesity, and 27.9% of subjects in this study had metabolic syndrome. This study also suggests that there is a high risk of elevated systolic blood pressure and elevated fasting insulin in obese children aged 6 to 10 years; this risk increases as degree of obesity increases. While impaired fasting glucose, impaired glucose tolerance, and dyslipidemia are quite prevalent in this study population, the risk of these abnormalities does not appear to increase as the severity of obesity increases. The prevalence of insulin resistance may be higher in females than in males, and impaired fasting glucose may be higher in males than in females.

This study also suggests that current recommendations for screening of metabolic abnormalities in obese school-age children are not sufficiently aggressive. The International Diabetes Federation's definition of the metabolic syndrome does not include children under the age of 10, and the Expert Committee does not recommend any biochemical assessment for children younger than 10 years. The prevalence of impaired glucose metabolism, insulin resistance, and dyslipidemia, however, is significant in this population, and screening for these abnormalities in children under the age of 10 is warranted.

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Appendix A: Acknowledgements

Thank you to my Culminating Experience committee, including Dr. James Ebert, Dr. Naila Khalil, and Dr. Miryoung Lee, for sharing your time and expertise in the creation of this project. I greatly appreciate the kind and patient way in which you guided and challenged me throughout this process, and look forward to working with all of you in the future. In addition, thank you to my wonderful family and friends for your love, support, and encouragement throughout the MPH program, particularly as I was completing this project.

Appendix B: IRB Approval Letter

The Children's Medical Center of Dayton IRB
One Children's Plaza
Dayton, Ohio 45404-1815
(937) 641-4218

March 3, 2011

Leah Sabato, R.D., L.D.
Clinical Dietitian
3 W and Lipid Clinic
The Children's Medical Center of Dayton
One Children's Plaza
Dayton, OH 45404

RE: Your memo of 2/22/2011 ***IRB Full Approval of New Research Study***
Dayton Children's study number 2011-005: Prevalence of Metabolic Abnormalities in Children with Varying Degrees of Obesity

Dear Ms. Sabato:

Thank you for your response to the IRB 2/9/11 request for additional information related to the new study listed above. Your study is eligible for expedited review under FDA and DHHS (OHRP) Category 5 criteria.

Item reviewed:
- Verification of CITI human subject research training for Naila Khalil, Ph.D., Sub-Investigator

This is to confirm that your application is now fully approved.

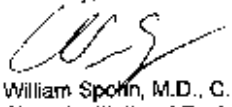
Items Approved:
- IRB Petition for Approval of Research Involving Human Subjects (Dated 1/11/2011)
- Waiver of Informed Consent Request (Dated 1/11/2011)
- Study Protocol (Dated 1/12/2011)
- Worksheet (Dated 2/8/2011)

You are granted permission to conduct your study as most recently described effective immediately. The study is subject to continuing review on or before **3/2/2012**, unless closed before that date. If you plan to continue the study one year from now, please submit for continuing review 60 days prior to termination.

The FDA requires you to notify the IRB of any change of investigator or site location, SAEs, significant protocol deviations, or termination of the study.

Please note that any changes to the study as approved must be promptly reported and approved. Some changes may be approved by expedited review; others require full board review. Contact Bev Corner (937-641-4218; fax 937-641-3201; email: CornerB@childrensdayton.org) if you have any questions or require further information.

Sincerely,



William Spohn, M.D., C.I.P.
Chair, Institutional Review Board

Appendix C: Public Health Competencies Met

The following Tier One Public Health Core Competencies were achieved during completion of this Culminating Experience project:

Analytical/Assessment Skills

- Identifies the health status of populations and their related determinants of health and illness.
- Describes the characteristics of a population-based health problem.
- Uses methods and instruments for collecting valid and reliable quantitative and qualitative data.
- Recognizes the integrity and comparability of data.
- Identifies gaps in data sources.
- Adheres to ethical principles in the collection, maintenance, use, and dissemination of data and information.
- Describes the public health applications of quantitative and qualitative data.
- Uses information technology to collect, store, and retrieve data.

Communication Skills

- Communicates in writing and orally, in person and through electronic means, with linguistic and cultural proficiency.
- Conveys public health information using a variety of approaches.
- Participates in the development of demographic, statistical, programmatic, and scientific presentations.

Community Dimensions of Practice Skills

- Recognizes community linkages and relationships among multiple factors (or determinants) affecting health.

Public Health Sciences Skills

- Describes the scientific evidence related to a public health issue, concern, or intervention.
- Retrieves scientific evidence from a variety of text and electronic sources.
- Discusses limitations of research findings.
- Partners with other public health professionals in building the scientific base of public health.